b) Oral fenfluramine dilated pupils in controls. This dilatation was statistically significant at 4, 6 and 8 h after the drug with p-value 0.05, 0.01 and 0.05 respectively. There was no significant dilatation of the pupils of IH sufferers after fenfluramine. The difference between the headache and control groups was statistically significant 4, 6 and 8 h after the drug (figure 2).

Discussion. The mydriatric hyper-reactivity to direct alpha adrenoceptor stimulating agent, phenylephrine, seems to indicate a supersensitivity of iris adrenergic receptors in IH.

Fenfluramine mydriasis in controls was similar to that reported by others[7] but in IH sufferers it was significantly less. This difference could be due to a more rapid plasma clearance of this drug or to a changed reactivity of the iris. Fenfluramine precipitates headache[8,9] convincingly by acting on the monoamine turnover[10]. In animals it exhibits peripheral cardio-vascular effects mainly by displacing noradrenaline stores at the adrenergic nerve terminal[11]. If the scarce fenfluramine-induced mydriasis in IH sufferers is due to a poor effect of the drug on the pupil, a reduced release or availability (or both of them) of noradrenaline in the iris nerve terminal can be hypothesized.

In conclusion: We observed on the one hand the hyperreactivity of the iris to an alpha adrenoceptor stimulator, phenylephrine, and on the other a hyporeactivity to a noradrenaline releaser, fenfluramine. Both these suggest a condition of supersensitivity caused by a deficiency of the specific transmitter at the iris adrenergic neuronal site in the IH sufferer.

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Effects of alpha- and beta-adrenergic blockers on the actions of noradrenaline on body temperature in the newborn guinea-pig

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Summary. The effect of NA injected into the lateral cerebral ventricle on T_c was blocked by alpha-adrenergic receptor blockers, but not by beta-receptor blockers, whereas the effect of systemically administered NA was blocked by i.p. administered beta-receptor blockers, but not by alpha-blockers.

Noradrenaline (NA) injected s.c., i.m., i.v. or into the lateral cerebral ventricle increased oxygen consumption and colonic temperature in newborn animals[2–8]. The effect of NA applied centrally[3–5], as well as systemically[7,8], decreased with age and practically disappeared at the age of 3–4 weeks. In contrast, adrenaline having an effect of only a fraction that of NA in the newborn guinea-pig[7], retains its effectiveness on metabolic rate throughout life[9]. For a more penetrating analysis, both NA and the adrenergic blocking drugs were administered systemically and centrally.

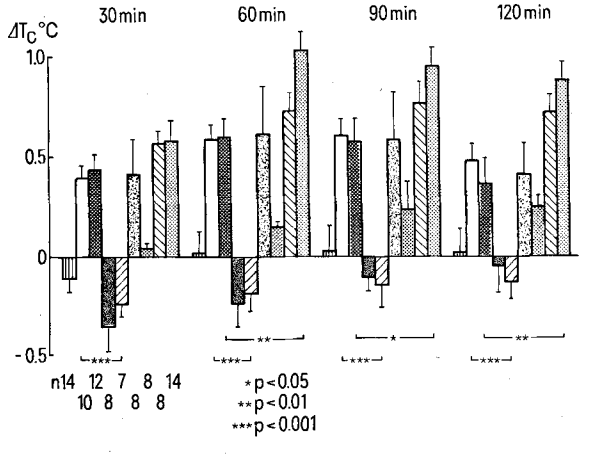

Fig. 1. The effect of 20 µl physiological saline i.c.v. (▥), 100 µg/kg NA i.m. (□), 10 µg NA i.c.v. (■), 1 mg/kg propranolol i.p. (▩), 1 mg/kg propranolol i.p. + 100 µg/kg NA i.m. (▨), 1 mg/kg propranolol i.p. + 10 µg NA i.c.v. (▤), 30 µg propranolol i.c.v. (▩), 30 µg propranolol i.c.v. + 100 µg/kg NA i.m. (▧) and 30 µg Propranolol i.c.v. + 10 µg NA i.c.v. (▤) on colonic temperature 30, 60, 90 and 120 min after NA.

Materials and methods. Colonic temperature (Tc) was measured by copper-constantan thermocouples in a depth of 6 cm at an ambient temperature of 30 °C in unanaesthetized guinea-pigs aged 1–12 days. This age was chosen because within this range the decrease in the effect of NA could be demonstrated, and the increase in Tc was still consistently present at the age of 12 days[3]. The drugs were injected either i.p., i.m., or into the lateral cerebral ventricle (i.c.v.) through the soft skull. Alpha- and beta-adrenergic receptor blockers were injected 30 min before NA. Injections of physiological saline served as controls.

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The drugs used were: L-noradrenaline bitartarate (Serva), phentolamine HCl (Ciba-Geigy) and D,L-propanolol (I.C.I.), the doses are expressed in the term of the salts. Student t-test was used for evaluation.

Results. Sham injections and physiological saline had no significant effect on colonic temperature. Propranolol i.p. or phentolamine i.p. alone induced a fall in Tc and at the moment of NA injection Tc-s were lower than initially. 1 mg/kg propranolol blocked the effect of 100 µg/kg NA i.m., whereas the effect of 10 µg NA injected i.c.v. was unaffected. 30 µg propranolol injected into the lateral cerebral ventricle had no effect on the action of systemically administered NA and did not decrease the effect of NA injected into the ipsilateral or contralateral cerebral ventricle (figure 1). Practolol had the same effect as propranolol. 1 mg/kg phentolamine i.p. did not alter the effect of 100 µg/kg NA i.m., whereas it decreased the effect of 10 µg NA i.c.v., 30 µg phentolamine i.c.v. had no effect on the action of systemically administered NA, whereas the effect of 10 µg NA i.c.v. was blocked completely (figure 2). Phenoxybenzamine and ergotamine acted as phentolamine.

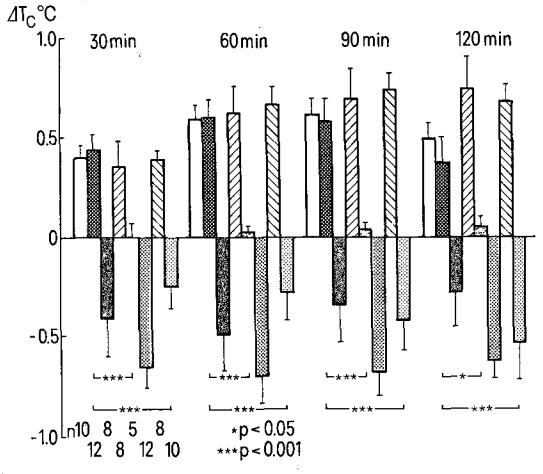

Fig. 2. The effect of 100 µg/kg NA i.m. (□), 10 µg NA i.c.v. (■), 1 mg/kg phentolamine i.p. (▩), 1 mg/kg phentolamine i.p. + 100 µg/kg NA i.m. (▨), 1 mg/kg Phentolamine i.p. + 10 µg NA i.c.v. (▩), 30 µg phentolamine i.c.v. (▩), 30 µg phentolamine i.c.v. + 100 µg/kg NA i.m. (▨) and 30 µg phentolamine i.c.v. + 10 µg NA. i.c.v. (▩) on colonic temperature 30, 60, 90 and 120 min after NA.

Discussion. NA elicited a rise in Tc in the newborn guinea-pig, independently of the route of administration. The mechanism of action was, however, not identical.

Beta-adrenergic blockers i.p. blocked the effect of systemically administered NA, implying the effect of NA was mediated by peripheral beta-adrenergic receptors. The effect of centrally applied NA was, however, not inhibited by i.p. administered beta-blockers, and beta-blockers injected into the lateral cerebral ventricle even enhanced the effect of NA. This observation indicates that, in contrast to systemically administered NA, the effect of centrally applied NA on Tc is not being mediated by beta-adrenergic receptors.

Alpha-adrenergic receptor blockers administered i.p. or i.v. failed to block the effect of systemically administered NA. In contrast, the effect of NA injected into the lateral cerebral ventricle was diminished by i.p. injected, and blocked by i.c.v. administered alpha-adrenergic blockers, indicating that the effect of centrally applied NA is mediated by central alpha-adrenergic receptors.

Despite the fact that the magnitude of the response to NA decreased with age, the effects of both alpha- and beta-blockers were not subjected to change with age up to the age of 12 days.

In vitro mutagenicity of the soil nematicide 1,3-dichloropropene

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Summary. The cis- and trans-isomers of 1,3-dichloropropene have been tested in the Ames mutagenicity assay system on Salmonella typhimurium tester strain TA 1535. Both isomers have been found to be mutagenic even without microsomal activation.

Some chlorinated olefines have recently been identified as carcinogens and/or mutagens, like vinyl chloride in experimental animals[1-3] and man[4], vinylidene chloride and 2-chlorobutadiene in in vitro mutagenicity testing[5,6], trichloroethylene in intact animal carcinogenicity testing[7] and in in vitro mutagenicity test[8]. The hypothesis has been promoted that all these compounds are activated in mammalian metabolism to electrophilic epoxides which may easily react, by alkylation, with essential cellular macromolecules[9,10]. A similar mechanism was suspected to prevail with 1,3-dichloropropene (1,3-DCP), a compound used as soil nematicide in agriculture[11]. To test this hypothesis, we used the Ames mutagenicity assay system[12].

The technical product of 1,3-DCP usually consists of a mixture of the cis- and trans-isomers with a small amount of 3.3-dichloropropene as an impurity. We have tested both the cis- and trans-isomers of 1,3-DCP. Purity according to GC-analysis: cis-1,3-DCP 99.97% (contaminants: 0.01% 3,3-dichloropropene-1, 0.02% 1,2-dichloropropane); trans-1,3-DCP 97.46% (contaminants: 1.32% 3,3-dichloropropene-1, 0.37% cis-1,3-DCP, 0.85% 'heavy ends'). Both isomers have been found to be mutagenic (table). Salmonella thyphimurium tester strains TA 1535, TA 1537 and TA 1538 all gave positive results. The data presented in this communication were obtained with TA 1535 which can detect mutagens causing base pair substitution.

The table shows the typical result of 1 out of several assays we made to prove the mutagenicity of 1,3-DCP. All assays gave essentially similar results: Both isomers of 1,3-DCP are mutagenic, even without microsomal activation, the cis-isomer being more active than the trans-isomer by the factor of about 2. There is also a significant difference in the survival rate of the bacteria exposed to varying concentrations of both isomers. At all concentrations tested, survival rates of cells exposed to cis-DCP are generally lower than those of bacteria exposed to trans-DCP. Concentrations of 2 µl/ml or more cause a drop of the survival rate to less than 1%, both in the case of cis- and trans-DCP.